In This Issue

Cell

De Novo Mutations at Hotspots

PAGE 1431

Michaelson et al. carry out whole-genome sequencing of monozygotic twins with autism spectrum disorders (ASD) and their parents and find that mutation rates vary by up to 100-fold throughout the genome. The identified mutational hotspots that are correlated with particular intrinsic characteristics of the DNA sequence and chromatin structure and are characteristic of genes involved in ASD and other diseases. The findings implicate hypermutability as a significant factor shaping human genetic variation and disease risk.

Wnt Caught Smuggling Hippo Parts

PAGE 1443 and PAGE 1457

Wnt signaling stabilizes the transcriptional coactivator β-catenin, which forms a complex with TCF4 to regulate target genes. Now, the transcriptional coactivators TAZ and YAP1 are identified as effectors of Wnt signaling, independent of their established roles in Hippo signaling. Azzolin et al. show that TAZ stabilization, as part of a complex with β-catenin, is a key feature of Wnt signaling. Rosenbluh et al. identify an alternative transcriptional complex composed of YAP1, β-catenin, and TBX5 that is essential for the proliferation and tumorigenicity of β-catenin-driven cancer cell lines.

Double-Strand Breakthrough

PAGE 1474

Ligase IV is a key factor in double-strand break (DSB) repair via nonhomologous end-joining (NHEJ). Srivastava et al. identify a small molecule inhibitor of Ligase IV that promotes the accumulation of DSBs to trigger cell death. This is shown to impede tumor progression in mice and improve the efficacy of DSB-inducing agents used for chemotherapy.

Piwi, If the Cap Fits…

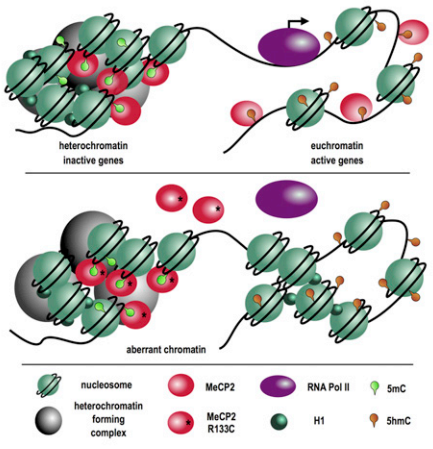
PAGE 1488

RNA polymerase II (Pol II) produces 18–40 nt capped small RNAs (csRNAs) of mysterious function that are often expressed bidirectionally at promoters. Using an efficient enzymatic method, CapSeq, for 5′-anchored Pol II transcription profiling, Gu et al. identify Pol II transcription start sites in *Caenorhabditis elegans*. Interestingly, they show that csRNAs expressed at promoters genome-wide are the precursors for Piwi-interacting RNAs (piRNAs), nearly doubling the number of piRNAs available to promote silencing of foreign nucleic acid sequences.

Usher for Electron Transport Chain Assembly

PAGE 1528

Mitochondrial respiratory chain complexes are assembled from proteins translated in the cytoplasm and in the mitochondria. Mick et al. show that the mitochondrial inner membrane translocase subunit TIM21 ushers cytoplasmically translated components of electron transport chain complexes (ETCs) away from the translocase and promotes their integration into ETC complex assembly intermediates that also contain mitochondrially translated subunits.



Message in a Bottle for Tumor Cells

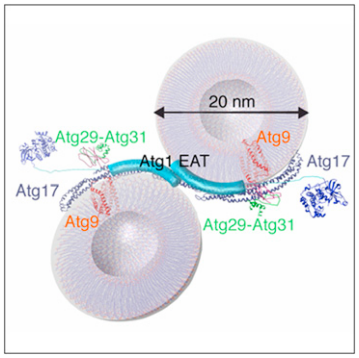
PAGE 1542

Luga et al. provide new insight into how stromal cells in the tumor microenvironment can stimulate primary tumors into metastatic behavior. The authors show that Wnt11-containing exosomes secreted by fibroblasts act on neighboring breast cancer cells to activate the planar cell polarity pathway, promoting motility and invasive behavior.

Rett's-Related Reader for 5hmC

PAGE 1417

A genome-wide analysis by Mellen et al. of 5hmC, 5mC, and gene expression in neuronal subtypes in vivo reveals an enrichment of 5hmC in active genes. They further show that MeCP2 protein recognizes and binds 5hmC and 5mC and that a mutation in MeCP2 that causes Rett syndrome preferentially inhibits 5hmC binding.



Crescent Rolls Up Autophagosomes

PAGE 1501

During macroautophagy, a phagophore forms as vesicles nucleate at the preautophagosomal structure (PAS). Ragusa et al. present a structural model of the PAS in which dimerization of the Atg17-Atg31-Atg29 complex is required for PAS formation. The crescent-shaped dimers assemble with Atg1, which binds to and tethers highly curved vesicles, suggesting a mechanism for initiating autophagosomal biogenesis.

Encouraging a Clingy Receptor to Play the Field

PAGE 1557

HLA-DM catalyzes the binding of microbial peptides to HLA-DR, the MHC class II cell-surface receptor, which subsequently presents antigen to T cells. Crystal structures of the HLA-DM-HLA-DR complex presented by Pos et al. reveal how DM changes the conformation of DR to allow it to rapidly sample peptides and only form lasting interactions with those of very high affinity.

Speeding to Steady State

PAGE 1569

Signaling circuits often face a fundamental tradeoff between accelerating their response speed while maintaining final levels of an output protein below a cytotoxic threshold. Teng et al. characterize an accelerator circuit that speeds the rate of gene expression without amplifying steady-state expression levels. This circuit operates in the human herpes virus cytomegalovirus where it confers a replicative fitness advantage for infected cells.

Converging on Synapse Elimination in Autism

PAGE 1581

Elimination of excitatory synapses is a critical process for experience-dependent refinement of neuronal circuits during brain development, learning, and memory. Tsai et al. provide evidence for a functional convergence for multiple autism-linked genes in synapse elimination through the ubiquitination and degradation of the postsynaptic scaffolding protein PSD-95.

T2D Risk—Liver Gets a New Look

PAGE 1595

Single-nucleotide polymorphisms in *TCF7L2* (encoding the Wnt effector TCF4) are the strongest genetic risk factors for type 2 diabetes. Most studies on *TCF7L2* have focused on β cells. However Boj et al. now show that genetically removing TCF4 from β cells in mice has no effect, whereas manipulating TCF4 levels in liver induces major changes in metabolism. After birth and during fasting, Wnt/TCF4 directly activates a metabolic gene program in liver, suggesting a new perspective for the human risk alleles.

Setting the Nucleosomal Stage for Differentiation

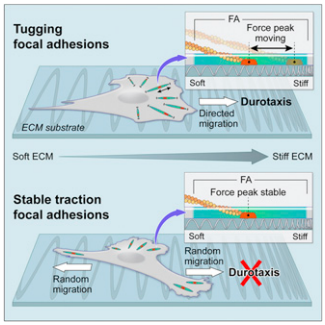
PAGE 1608

Li et al. demonstrate that dynamic, genome-wide repositioning of nucleosomes accompanies the differentiation of embryonic stem cells into prehepatic endoderm. Foxa2 collaborates with H2A.Z to target nucleosomes for removal by ATP-dependent chromatin remodelers during the differentiation process to foster gene expression.

Refractory Cells Get with the Reprogram

PAGE 1617

The generation of iPSCs is extremely inefficient, complicating mechanistic dissection of the process. Polo et al. sort fibroblasts in different stages of the reprogramming process, including those refractory to reprogramming, and characterize them molecularly. The authors identify genes that enhance reprogramming and are able to generate iPSCs from the refractory population.



Focal Adhesions Show Their Stiff Upper Lip

PAGE 1513

Cells can sense differences in the stiffness of their microenvironment and move towards stiffer areas during normal development and wound healing and also during cancer metastasis. Plotnikov et al. show that cells use focal adhesions to tug repeatedly at—and thus test—the local stiffness of the microenvironment in order to guide cell movement towards stiffer areas. They identify pharmacological and genetic perturbations that selectively activate or inactivate tugging, which may enable control of cell movement in normal and pathological states.